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09/811,131	03/14/2001	Christen M. Anderson	660088.420D1	7827

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EXAMINER
SCHNIZER, HOLLY G

ART UNIT	PAPER NUMBER
1653	8

DATE MAILED: 07/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/891,431	Applicant(s) ANDERSON ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

FILE COPY

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-112* is/are pending in the application.

4a) Of the above claim(s) *1-74,85-103 and 105-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *75-84 and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 7 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 5 and 27, drawn to recombinant expression constructs encoding an ANT1 polypeptide, classified in class 435, subclass 320.1.

II. Claims 6 and 28, drawn to recombinant expression constructs encoding an ANT2 polypeptide, classified in class 435, subclass 320.1.

III. Claims 7 and 29, drawn to recombinant expression constructs encoding an ANT3 polypeptide, classified in class 435, subclass 320.1.

Claims 1-4, 8-26, and 30-41 link Groups I-III. These linking Claims will be examined with respect to the subject matter of the Invention of Groups I, II, or III, if one of these Groups is elected.

IV. Claim 44 drawn to ANT1 polypeptide, classified in class 530, subclass 300.

V. Claim 45, drawn to ANT2 polypeptide, classified in class 530, subclass 300.

VI. Claim 46, drawn to ANT3 polypeptide, classified in class 530, subclass 300.

Claims 42-43 and 47-57 link Groups IV-VI. These linking Claims will be examined with respect to the subject matter of the Invention of Groups IV, V, or VI, if one of these Groups is elected

VII. Claim 60, drawn to a method of determining the presence of an ANT1 polypeptide in a sample, classified in class 435, subclass 7.1.

VIII. Claim 61, drawn to a method of determining the presence of an ANT2 polypeptide in a sample, classified in class 435, subclass 7.1.

IX. Claim 62, drawn to a method of determining the presence of an ANT2 polypeptide in a sample, classified in class 435, subclass 7.1.

Claims 58-59, 63-74 link Groups VII-IX. These linking Claims will be examined with respect to the subject matter of the Invention of Groups VII-IX, if one of these Groups is elected.

X. Claims 75-84 and 104 drawn to a method for identifying an agent that binds to an ANT polypeptide and an assay plate for high throughput screening of candidate agents that bind ANT polypeptide, classified in class 435, subclass 7.1.

XI. Claims 85-103 and 107-111, drawn to an ANT ligand, classified in class 530, subclass 300.

XII. Claims 105-106 drawn to a method of targeting a polypeptide to the mitochondrial membrane, classified in class 435, subclass 317.1.

XIII. Claim 112, drawn to a method of treatment comprising administering a pharmaceutical composition comprising an ANT ligand, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I-III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the genes encoding ANT1, ANT2, and ANT3 are distinct and encode proteins having different structures, functions, and which are expressed in different tissues. For example, ANT1 is expressed in heart and skeletal muscle; ANT2 appears to only be expressed in neoplastically transformed cells with high glycolytic rates, in tumors, and tumoral cells; and ANT3 is ubiquitously expressed (Giraud et al. J. Mol. Biol. (1998) 281: 409-418, see p. 409, col. 2; ref. BH in IDS filed 3-16-01 as Paper No. 6). Moreover, while ANT1 and ANT3 export ATP synthesized in the mitochondria to the cytosol, ANT2 appears to translocate glycolytic ATP synthesized in the cytosol, to the mitochondrial matrix (see Giraud et al. p. 413, Col. 2). Because the ANT protein isoforms are expressed in different tissues and have different structures and functions, the polynucleotides encoding them are independent and distinct, one from the other, and could be used for different purposes and have different effects.

The inventions of Groups IV-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the ANT1, ANT2 and ANT3 polypeptides are distinct are unrelated for the reasons stated in the preceding paragraph. ANT1, ANT2 and ANT3

proteins have different structures, functions, and are expressed in different tissues. Because the ANT protein isoforms are expressed in different tissues and have different structures and functions, they are independent and distinct, one from the other, and could be used for different purposes and have different effects.

The inventions of Groups I-VI and XI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the expression constructs and host cells of Inventions I-III, the polypeptides of Inventions IV-VI, and the ligands of Invention XI have different biological structures and different functions. In addition, subject matter of each Group is not coextensive and thus the search for each would constitute a serious burden upon the examiner. For example, the expression constructs of Group I would require consideration of its use for processes other than the production of the protein, such as nucleic acid hybridization assay and the protein would required searches of literature wherein the protein was isolated from its source rather than recombinantly produced using the polynucleotide. Thus, Groups I-III require considerations which are not required in the search for proteins of Groups IV-VI and Groups IV-VI require considerations which are not required in the search for the polynucleotides of Groups I-III. Likewise, the polypeptides of Groups IV-VI have different functions and are used for different purposes than the ligands of Group XI.

The expression vectors of Groups I-III are unrelated to the methods of Groups VII-X and XIII. Inventions are unrelated if it can be shown that they are not disclosed

as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the expression vectors of Groups I-III are not made by nor used in the protein binding assays of Groups VII-X or the method of treatment using an agent that binds ANT of Group XIII. Inventions I-III and XII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the expression vectors of Groups I-III can be used in a method of making the polypeptides or in hybridization assays, which are materially different processes than the method of targeting the ANT polypeptide to the mitochondrial membrane of Invention XII.

The ANT polypeptides of Groups IV-VI are unrelated to the methods of Groups VII-IX and XIII. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the polypeptides of Groups IV-VI are not made by nor used in the method of screening using an ANT ligand of Groups VII-IX or the method of treatment using an agent that binds ANT of Group XIII.

Inventions IV-VI are related to the methods of Groups X and XII as product and process of use. The inventions can be shown to be distinct if either or both of the

following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the polypeptides of Groups IV-VI can be used in a method of making an antibody or in activity assays, which are materially different methods than the protein binding assays and method of treatment using an ANT ligand of Groups X and XIII.

The ANT ligands of Group XI are unrelated to the methods of Groups X and XII. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the ligands of Group XI are not made by nor used in the method of screening using an ANT polypeptide of Group X or the method of targeting an ANT polypeptide to the mitochondrial membrane of Group XII.

The ligand of Invention XI is related to the methods of Inventions VII-IX and XIII as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the ligand of Invention XI could be used in a method of inhibiting the activity of the ANT polypeptides, which is materially different than the method of screening for an ANT polypeptide of Groups VII-IX or the method of treatment of Group

XIII. In addition, the ligand could be used in a method of diagnosis, which is materially different from the methods of screening and treatment of Inventions VII-IX and XIII.

The methods of Groups VII-IX are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the ANT polypeptides are expressed in different tissues and have different structures and functions. Therefore, the different screening methods could not be used together and each method would have different endpoints since each would likely bind ligands of differing structure.

The methods of Inventions VII-X, XII, and XIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the methods of Inventions VII-X, XII, and XIII are materially different each from the other because each is practiced with materially different process steps, technical considerations, and reagents and each is practiced to accomplish a distinct goal.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has

prima facie shown a serious burden of search (see MPEP § 803). Therefore, the initial requirement of restriction for examination purposes as indicated is proper.

During a telephone conversation with Stephen Rosenman on June 18, 2003, a provisional election was made without traverse to prosecute the invention of Group X, Claims 75-84 and 104. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-74, 85-103, and 105-112 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Status of the Claims

Claims 1-112 are pending. Claims 1-74, 85-103, and 105-112 are withdrawn from further consideration as being drawn to non-elected subject matter. Claims 75-84 and 104 will be examined on the merits in this Office Action.

Sequence Compliance

The disclosure is objected to because of the following informalities: There are no sequence identifiers for the sequences listed in Figures 1A, 1B, and 2. Sequence information in the drawings must still be included in a "Sequence Listing" and the sequence identifier ("SEQ ID NO:X") must be used in the drawings or the Brief Description of the Drawings (see 37 C.F.R. 1.821 and MPEP 2429, 22nd paragraph). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 75-84, and 104 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The acronym, ANT, in independent Claims 75, 83, 84, and 104 is indefinite because ANT could refer to more than one type of polypeptide (for example, ant may also refer to an Na+/H+ antiporter). The dependent claims do not clarify this ambiguity. Therefore, correction of the independent claims to include the full name of the polypeptide followed by it acronym in parenthesis would overcome this rejection. Amendment of the independent claims would obviate the rejection for the dependent claims as well.

Claim 84 is indefinite because the method involves a comparison of the binding of detectable ANT ligand in the presence and absence of the agent but there is no step of contacting the biological sample containing the ANT with the ligand in the absence of an agent. This rejection could be overcome by amending line 4 of the claim to read ..."detectable ANT ligand in the absence or in the presence of a candidate agent".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 104 is rejected under 35 U.S.C. 102(b) as being anticipated by Neumann et al. (J. Immunol. (1994) 152: 343-350).

Neumann et al. discloses 96-well ELISA plates comprising an immobilized ANT polypeptide for screening of candidate agents that bind to an ANT polypeptide (antibodies). The immobilized ANT polypeptides of Neumann et al. are considered patentably indistinguishable from recombinant ANT polypeptides and also are considered variants of recombinant ANT polypeptides of other isoforms.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 75, 78, 79, and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roux et al. (Anal. Biochem. (1996) 234: 31-37; ref. CM of IDS of Paper No. 6) in view of Adrian et al. (Mol. Cell. Biol. (1986) 6(2): 626-634; ref. AH of IDS of Paper No. 6).

Roux et al. teaches a method for identifying an agent that binds to an adenine nucleotide translocator (ANT) polypeptide comprising contacting an agent (N-ATR or Mant-ATR) with muscle homogenate (containing cells expressing ANT or a biological sample containing ANT) under conditions and sufficient time to permit binding and detecting binding by fluorescence (see p. 35-36).

Roux et al. do not teach that the cells or biological samples used in the assay contain recombinant ANT.

However, Adrian et al. provides evidence that protocols for the recombinant expression of ANT in yeast cells were well known in the art at the time of the invention. Adrian et al. teaches the recombinant expression of ANT as a fusion protein to β-galactosidase in Saccharomyces cerevisiae.

Therefore, it would have been obvious to one of skill in the art at the time of the invention, that the method of Roux et al. could be improved by using cells recombinantly expressing the ANT polypeptide using the protocols for yeast expression of Adrian et al., rather than muscle homogenate. As discussed in Roux et al. (p. 36, paragraph bridging columns), those of skill in the art were interested in finding new probes for ANT (agents that bind ANT) that were convenient, reliable, and highly sensitive in order to quantify the amount of ANT in normal and pathological tissues. One of ordinary skill would have been motivated to use recombinant ANT expression as part of the method in order to allow for a greater number of candidate agents to be tested in a shorter period of time. Moreover, one of ordinary skill would have had a reasonable expectation of success in practicing the method of Roux et al. modified by using recombinant expression rather than muscle homogenates since Adrian et al. teaches successful protocols for recombinant expression of ANT in yeast. Thus, the claims are unpatentable over the prior art.

Claims 75-79 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roux et al. and Adrian et al. as applied to claims 75, 78, 79, and 83 above, and further in view of Tjaden et al. (J. Biol. Chem. (April 1998) 273(16): 9630-9636; ref. DL of Paper No. 6).

The teachings of Roux et al. and Adrian et al. have been described above.

Roux et al. does not teach recombinant expression of ANT.

Adrian et al. provides evidence that methods of recombinant expression of ANT were well known in the art at the time of the invention.

Tjaden et al. teaches the recombinant expression of a plant adenine nucleotide translocator which is considered a homologue to human ANT. Tjaden et al. teaches that heterologous expression of eukaryotic membrane proteins in E. coli was problematic because they were often toxic to the cell. However, Tjaden et al. teaches that a new strain of E. coli (C43, a derivative of E. coli strain BL21) had already been shown to allow overproduction of five highly hydrophobic membrane proteins from animal origins (p. 9634, Col. 2, 2nd paragraph). Tjaden et al. shows that this same E. coli strain could be used successfully to recombinantly produce a functional plant adenine nucleotide translocator. Tjaden et al. also refers to the successful recombinant expression of other ATP/ADP transporters such as that from the Gram-negative bacterium R. prowazekii (p. 9635, Col. 1, 1st paragraph) and they propose that this expression system could be used successfully for the recombinant expression of homologues from other sources (p. 9635, Col. 2, last paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Roux et al. by using cells that recombinantly express an ANT polypeptide as taught in Tjaden et al. The tools (host E. coli strain C43) for successful recombinant expression of eukaryotic membrane proteins were very well known in the art and successful recombinant expression of a close homologue to ANT had already been demonstrated. Therefore, one of ordinary skill would have had a reasonable expectation of success. Moreover, one of ordinary skill would have been motivated to modify the method of Roux et al. by using recombinant expression in E. coli cells because it would allow for faster and easier processing of a greater number of candidate binding agents at reduced cost as compared to the more cumbersome isolation of muscle homogenate or expression in yeast cells.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

HS
Holly Schnizer
July 8, 2003

Christopher S. Low

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